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Inverness Medical Innovations / WSGR
Wilson Sonsini Goodrich & Rosati, P.C.
650 Page Mill Road
Palo Alto, CA 94304

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RECORD OF ORAL HEARING

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JEFFREY R. DAHLEN, KENNETH F. BUECHLER
and GUNARS E. VALKIRS

Appeal 2008-1230
Application 09/835,298
Technology Center 1600

Oral Hearing Held: September 9, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
ERIC B. GRIMES, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANT:

Michael A. Whittaker, Esquire
WILSON, SONSINI, GOODRICH & ROSATI, P.C.
650 Page Mill Road
Palo Alto, CA 94304

P R O C E E D I N G S

MS. BOBO-ALLEN: Calendar No. 2, Appeal No. 2008-1230. Mr. Whittaker.

JUDGE SCHEINER: Good morning, Mr. Whittaker.

MR. WHITTAKER: Good morning. Let me find my glasses.

JUDGE SCHEINER: Whenever you're ready.

MR. WHITTAKER: Ready? Thank you for giving me the opportunity to be here. I'm Mike Whittaker. I'm representing the assignee, Inverness Medical Innovations, in today's appeal. And the topic of the claims that are at issue are -- have to do with risk stratification in Acute Coronary Syndromes.

Let me first talk a little bit about Acute Coronary Syndromes. Acute Coronary Syndromes are a spectrum of diseases that extend from one end, unstable angina, to, at the more extreme end, Q wave myocardial infarction. And they're an umbrella of diseases that are related by the fact that they're acute, meaning they're -- the incident is happening now, and they're all coronary related. Myocardial infarction is generally thought of in the art as meaning that there is necrosis going on in the heart; the heart muscle cells are dying. At the other end, at the end of angina, there is typically -- it's typically considered that there is not necrosis occurring at that time, and that's a condition that is more likely to resolve. So ACS patients are the kind of people that walk into a hospital having chest pain and shortness of breath. It's that classic presentation.

And there's generally two things that physicians want to know at that point. One is why is this person having chest pain. That's a diagnosis. And the other is, okay, once I know that this person is having an acute coronary syndrome event, is he somebody that's going to get into trouble; is he somebody that's going to die; do I need to get him into the cath lab; do I need to admit him to the hospital, or is this something that I can sit and

watch and then refer him back to his own physician. That's risk stratification; trying to identify those that are really at risk.

The present claims relate to the use of at least two markers for that risk stratification. One of those markers is a cardiac troponin. A cardiac troponin is a molecule in the heart muscle that consists of three polypeptide chains, two of which are cardiac specific, Troponin I and Troponin T. Troponin C is the same in skeletal muscle. So when you're looking at a cardiac event, you want to look at the cardiac-specific forms because you've got a lot more skeletal muscle than you do cardiac muscle. The other marker is BNP or a marker that's related to BNP calledNT pro BNP or Pre pro BNP.

JUDGE SCHEINER: Excuse me. You have a couple of claims where the marker -- you have the BNP, but the second marker can be something other than Troponin I or T. But was there an election of species or --

MR. WHITTAKER: There was an election of -- well, I mean, this case has been pending for a long time, as you probably saw.

JUDGE SCHEINER: Right.

MR. WHITTAKER: There's been a -- the claims have been allowed at least three times. There's been an interference that was resolved in our favor. There was a species election. After it came back from the Interference Board, it was allowed again, and then at that point an RCE was filed to get all of the evidence from the interference in. And at that point, the claims were rejected as being indefinite even though the language hadn't really changed from what had gone through an entire interference. Those questions were ultimately resolved, but then we were faced with this single

obviousness rejection. So there has been a species election here, but the claims, as drafted, are broader than that.

Now, BNP is synthesized as a large molecule, 108 amino acid Pro BNP molecule, which is then cleaved not quite in half. The N terminal portion of that cleavage is called NT pro BNP. The C Terminal portion of that molecule is called BNP. So they're all related. They're generated by the same biosynthetic event and they all give pretty much the same information.

The rejection in this case is an interesting one. This is one of those cases, I think, where it's true that you really have to look at the entire record as a whole, rather than just picking bits or pieces of it to understand the nonobviousness of this invention, and that's something I think the examiner has not done.

So if we turn to the rejection for a minute, the rejection begins with a reference to a patent by Jackowski, and Jackowski has to do with diagnosis, not prognosis. Jackowski is trying to identify patients who are having an MI.

JUDGE SCHEINER: Why don't we focus on Antman --

MR. WHITTAKER: Well, let me just focus on Jackowski for just a second because I think it gets to one problem the examiner has in this case. The examiner's initial premise in the rejection is that Jackowski teaches the invention substantially as claimed. Even though Jackowski is directed to diagnosis and Jackowski never mentions BNP or any of the BNP-related markers, that's the examiner's initial premise, is that Jackowski teaches the invention substantially as claimed. And that bias just colors the rest of the rejection.

So if we turn to the rest of the record, we can deal with Antman first. Antman looks -- Antman is a New England Journal article from 1996, and it looks at Troponin I in risk prediction in an ACS population, and whatit says is that if you have a Troponin I level greater than .4 nanograms per ml, you're at an increased risk of mortality as opposed to a level lower than that. And .4 nanograms per ml indicates that there is necrosis going on, because otherwise you would -- you don't just walk around with a troponin level like that. The only reason to have it is if cardiac muscle cells are dying. So what Antman is telling you is that Troponin I is a classic necrosis marker, and if you have ongoing necrosis, you have an increased risk of mortality.

The same year, in 1996 --

JUDGE SCHEINER: What were the patients that they looked at?

MR. WHITTAKER: They looked across the spectrum of ACS.

JUDGE SCHEINER: Okay.

MR. WHITTAKER: But their conclusion was that here's a Troponin I level that above this you have an increased risk. Later in 1996, there's an article by Arakawa, et al., which is not part of the rejection. Arakawa is looking at BNP in risk prediction after acute MI.

JUDGE SCHEINER: That was one of the references you submitted?

MR. WHITTAKER: That was one of the references that have been submitted, yeah. And it notes that BNP is predictive of risk after acute MI, and it states that BNP, like the other cardiac necrosis markers, is released from infarcted tissues. What that is telling the art is that BNP and Troponin I are both acting as necrosis markers, and they are both predictive of risk in a necrosis population in acute MI.

Now, the examiner ignored Arakawa -- the only reason I can imagine is because it doesn't fit the examiner's rejection -- and moved on to Richards, et al., which is a 1999 article. So we're three years after Antman and Arakawa. And what Richards says is that plasma BNP one to four days after an AMI predicts risk in that population. It's basically confirming what Arakawa had already shown.

Interestingly, Richards had troponin data on all of his patients. It's in his methods. He used it to identify those patients who were having an acute MI, because Troponin I is a necrosis marker. If you didn't have an elevated troponin, you weren't in his study, you weren't -- you didn't have an acute MI. So he had troponin and BNP data. He was looking at what BNP was independent of, and he says BNP, the risk predicted by BNP is independent of sex, age, clinical history, left ventricular ejection fraction, which is a measure of heart failure, and plasma noradrenaline. He never looked at troponin. If it was -- this is three years after both troponin and BNP are in the art as risk markers. If it was obvious to combine them, why didn't he combine them?

JUDGE SCHEINER: You're saying that's in the methods, that he had data --

MR. WHITTAKER: That's in his methods, that he had measured troponin on all of his patients and had them and used it to identify those who were having an acute MI.

JUDGE SCHEINER: Can we go back to Antman for a moment?

MR. WHITTAKER: Yes.

JUDGE SCHEINER: Why do you think that Antman said "our findings extend the observations on the benefits of measuring this marker to the entire range of Acute Coronary Syndromes"?

MR. WHITTAKER: Well, they are measuring in -- they are measuring across the range of Acute Coronary Syndromes. What they're telling you is measure across the range of Acute Coronary Syndromes and if necrosis is occurring, as measured by troponin, then you have an increased risk of mortality.

JUDGE SCHEINER: But isn't that saying that there's a benefit to measuring across the range?

MR. WHITTAKER: Well, I think it's --

JUDGE SCHEINER: Regardless of what the --

MR. WHITTAKER: I think what it's telling you is some of those patients that you think may be having -- that are not having an MI or having an MI, you're not recognizing it, because otherwise their troponin wouldn't be going up. A level of .4 nanograms per ml --

JUDGE SCHEINER: But your specification says --

MR. WHITTAKER: -- is an MI.

JUDGE SCHEINER: Doesn't your specification say -- and I'm not sure where. I believe it's around page 5 of your specification. Doesn't it say that prognosis doesn't necessarily refer to predicting an adverse outcome, but can also predict a favorable outcome?

MR. WHITTAKER: Yes, that is true.

JUDGE SCHEINER: So if Antman is looking across the range and only -- and saying that if you get a certain level, it's indicative of necrosis and a poorer prognosis?

MR. WHITTAKER: Yes. Yeah, and if you're not having necrosis --

JUDGE SCHEINER: Isn't the converse true?

MR. WHITTAKER: If you're not having necrosis, that's an indication of a better prognosis.

JUDGE SCHEINER: Which would -- right.

MR. WHITTAKER: Yes. Agreed.

JUDGE SCHEINER: Okay.

MR. WHITTAKER: Agreed. Now, so, what you have from Antman and Arakawa are that BNP and troponin are both acting like necrosis markers and they're both predictive of risk in that population. Richards, cited by the examiner, had the data and didn't combine them. A later publication in 2000 by Hassan, et al. extended Arakawa again. It looked at BNP increases in the heart using a thallium scan to distinguish between ischemic myocardium and necrotic myocardium. And Hassan indicates that BNP is only being released by the necrotic tissues, and not by the ischemic tissues. So what you have leading up to the invention is that BNP and troponin are both necrosis markers, and if you're having necrosis, your outcome is worse. If you're not having necrosis, then your outcome is better. I would agree with that.

The present invention, though, is different. The present invention says when you combine troponin and BNP, you find that BNP is actually

independent of troponin. It's not providing simply the same information that troponin is. It's not simply acting as a necrosis marker.

If you look at Jackowski, I mean, Jackowski puts two markers together for diagnosis. He's looking at markers that are elevated at different times. So one marker might be elevated at three hours while another marker isn't elevated until 12 hours. Both of those markers, though, are dependent on the same event. You're not having more of a heart attack if they're both ultimately elevated. You're still having a heart attack, it's just picking up at different times.

That's not what the data in the present specification says. The present specification says if you have an elevated troponin, you're at a risk -- you're at an increased risk of a bad outcome. If you have an increase in BNP, you're at an even greater risk, because it's independent, it's providing additional new information the troponin's not providing. And that's contrary to what Arakawa and Hassan were telling the art you would find.

JUDGE SCHEINER: So is it your position that it wouldn't be obvious to look for them at the same time in the same sample?

MR. WHITTAKER: I'm saying that there are secondary indicia of nonobviousness here. One of those secondary indicia is an unanticipated benefit to the combination. You would not have predicted from the art that if you measure both BNP and troponin you would get independent information from those two measurements. You would get the same information from those two measurements.

And the other is that BNP is predictive even in the absence of necrosis. That's contrary to what was taught in the art, that's contrary to Arakawa, and it's contrary to Hassan. BNP is --

JUDGE SCHEINER: Is that contrary to Antman, though? It says that if you don't see it, then you don't have necrosis, which would, again, lead to a better prognosis?

MR. WHITTAKER: Again, all that's telling you is are you having necrosis or not. Right? If you're having necrosis, you're at a worse -- you're in a worse state than if you're not. This is telling you that even in the case where you're not having necrosis, BNP can provide information on those patients who are also in trouble. Even in the absence of necrosis, it's predictive of a bad outcome.

JUDGE SCHEINER: Okay.

JUDGE GRIMES: But even if in the prior art they were understood to both be measurements of necrosis, wouldn't a high level of one -- a high level of both be a confirmation that would confirm getting more information than you would have had if you just measured one or the other?

MR. WHITTAKER: I always -- I hesitate to make a rejection that the examiner didn't make, but if I were structuring this rejection, that's how I would have structured it. I would have said they're both useful for the same thing, so it's obvious to combine them as confirmation of one another. That I think -- I think there probably is a prima facie case of obviousness here, and that's it; that you can combine them because they're useful for the same thing. And then you start looking at the secondary indicia of nonobviousness.

So given that we have a prima facie case, has the secondary indicia overcome it? And the secondary indicia are the unexpected finding that BNP is independent of troponin and provides additional information; that BNP is predictive even in the absence of necrosis. And then -- okay.

JUDGE GRIMES: So that would mean that it would be predictive of the prognosis even in patients who aren't having an MI, as it were?

MR. WHITTAKER: Yes, that's exactly what that means.

JUDGE GRIMES: But if they're both predictive of prognosis in someone who's having an MI, then don't you have at least one obvious embodiment in the scope of what you're claiming?

MR. WHITTAKER: You have -- well, I think you overcome that prima facie case with the secondary indicia, is what I think. And if we look at that, when the data from the specification was published, it was published in the New England Journal. The New England Journal doesn't just publish anything. The New England Journal is probably the most prestigious journal in the United States, medical journal, and it was published in the New England Journal. It was not only published in the New England Journal, it was published with an accompanying editorial trumpeting the invention as being new markers of ischemia and that -- and pointing out that when you combine them, you get independent information, and that it's predictive even in the absence of necrosis. So that's a secondary indicia of a claim.

JUDGE SCHEINER: I think the point, though, was that the secondary indicia wouldn't apply to the patient who presents with MI, which is within the scope of your claim. So there's an embodiment covered by your claim, that the secondary indicia --

MR. WHITTAKER: Why don't -- why wouldn't they --

JUDGE SCHEINER: -- it wouldn't apply to. Because the art already says that it's predictive in those cases where you have necrosis.

MR. WHITTAKER: The art --

JUDGE SCHEINER: Did I understand what you --

MR. WHITTAKER: The art doesn't tell you that when you combine them you're going to get new information that you never got from one or the other. That's what you get from combining them.

JUDGE SCHEINER: No, I understand that part. We're just trying to determine whether the claims encompass an obvious embodiment that's not overcome or rebutted by the secondary indicia.

MR. WHITTAKER: I think we all have to agree that even a prima facie obvious embodiment can be overcome by secondary indicia of obviousness, can it not?

JUDGE SCHEINER: Yes.

MR. WHITTAKER: So, so if --

JUDGE GRIMES: But the problem that we're having is it sounds like to us -- or at least to me like what you're saying is it was obvious to measure these two markers -- in someone who's having an MI, it's obvious to measure these markers and it would be recognized as predictive of prognosis for someone having an MI. And what you've discovered is that it's predictive for prognosis for a larger group of people. The problem being that your larger group of people still has the people having an MI within.

MR. WHITTAKER: But it's also unpredictably better in the MI population. It's not simply that combining them is confirmatory, it's unpredictably better in that population.

JUDGE GRIMES: Okay. I understand your argument now.

JUDGE SCHEINER: Is that discussed in your specification?.

MR. WHITTAKER: It's discussed in the specification that they are independent. It is confirmed in the -- in various references filed after that, and ultimately, all of this -- I mean, we are -- so, I mean, Richards was three years after BNP entered. And again, if it was obvious to combine them, why didn't he combine them? He -- had all of the data and was looking for markers that were -- that BNP was independent of. He didn't seem to think it was obvious to combine them.

Ultimately, this was -- this invention was turned into a recommendation for clinical practice, and that's in the Silver BNP Consensus Panel document, which ultimately was published in 2004, which points out -- cites the New England Journal article that publishes our data, indicates that this is predictive across the full spectrum, indicates that it is independent, that BNP measurements are independent of troponin, and tells clinicians to start using this invention. Again, that -- what you have is secondary indicia of unanticipated advantages, copying a claim and adoption, ultimately, into clinical practice. And my argument is that all of that together -- when you look at the entire package, the conclusion is that this is a nonobvious invention. Even in the case where there was a -- where you can establish a prima facie case that it was obvious in the MI population,

you're still getting information that you didn't predict you would get, and it was ultimately copied and adopted into the art.

JUDGE SCHEINER: I think we understand the issues. Do you have any --

JUDGE MILLS: I just have one last question. Are you aware if any of this came up in the interference at all, any of the --

MR. WHITTAKER: All of this --

JUDGE MILLS: -- that it's obvious in the context of the --

MR. WHITTAKER: Obviousness, I mean, obviously -- obviously. Both parties thought this was a nonobvious invention. And again I'll point out, this was allowed three times in the Patent Office and went through an entire interference proceeding and then came back in and now it's suddenly -- it was suddenly obvious at that point.

JUDGE SCHEINER: Antman and Richards were in the case from the beginning. I saw that they're -- I know that they're cited in the spec. Were they -- in an IDS?

MR. WHITTAKER: They were in the case from the beginning, yeah.

JUDGE SCHEINER: Early on?

MR. WHITTAKER: Um-hum.

JUDGE SCHEINER: And -- okay.

MR. WHITTAKER: In the end, I think the examiner just avoided considering any of the secondary indicia. It's hard to -- I mean, now we're sitting here talking about it I think as it should have been discussed during prosecution. But at the time the examiner was considering this, all the examiner did was find reasons to avoid considering it. The examiner took

the position, for example, that there was no evidence in the record that BNP was predictive across the full spectrum of ACS, and that's just baffling, to take that position.

JUDGE SCHEINER: Okay, well, we'll look at everything that the examiner looked at or didn't look at.

MR. WHITTAKER: And it's -- again, if -- it's difficult to limit claims in the face of a rejection that isn't properly formed, I think. So the claims are what they are, and I think the secondary indicia stand for themselves.

JUDGE SCHEINER: I think we understand --

MR. WHITTAKER: Okay. Thank you.

JUDGE SCHEINER: Thank you for coming in.

(Whereupon, the hearing concluded at 9:48 a.m. on September 9, 2008.)